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Abstract
Maintenance of circadian alignment between an organism and its environment is essential to ensure metabolic homeostasis. Synchrony is achieved by cell autonomous circadian clocks. Despite a growing appreciation of the integral relation between clocks and metabolism, little is known regarding the direct influence of a peripheral clock on cellular responses to fatty acids. To address this important issue, we utilized a genetic model of disrupted clock function specifically in cardiomyocytes in vivo (termed cardiomyocyte clock mutant (CCM)). CCM mice exhibited altered myocardial response to chronic high fat feeding at the levels of the transcriptome and lipidome as well as metabolic fluxes, providing evidence that the cardiomyocyte clock regulates myocardial triglyceride metabolism. Time-of-day-dependent oscillations in myocardial triglyceride levels, net triglyceride synthesis, and lipolysis were markedly attenuated in CCM hearts. Analysis of key proteins influencing triglyceride turnover suggest that the cardiomyocyte clock inactivates hormone-sensitive lipase during the active/awake phase both at transcriptional and post-translational (via AMP-activated protein kinase) levels. Consistent with increased net triglyceride synthesis during the end of the active/awake phase, high fat
feeding at this time resulted in marked cardiac steatosis. These data provide evidence for direct regulation of triglyceride turnover by a peripheral clock and reveal a potential mechanistic explanation for accelerated metabolic pathologies after prevalent circadian misalignment in Western society.